TURKISH INFLAMMATORY BOWEL DISEASE SOCIETY RECOMMENDATIONS ON SELECTED TOPICS OF ULCERATIVE COLITIS
TÜRK İNFLAMATUVAR BARSAK HASTALIKLARI DERNEĞİNİN ÜLSERATİF KOLİT İLE İLGİLİ SEÇİLMİŞ KONULARDA ÖNERİLERİ

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Prevalence, predictive factors and ideal treatment of cytomegalovirus infection in IBD patients

İnflamatuvar barsak hastalığı olan kişilerde sitomegalovirus enfeksiyonunun prevalansı, prediktif faktörleri ve ideal tedavisi

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INTRODUCTION

Cytomegalovirus (CMV) infection is one of the most common infectious complications of immunosuppressive therapy, and it mainly occurs as a secondary infection in CMV-seropositive patients. Seropositivity is generally high in population-based screenings, up to 100% (1). In immunocompetent subjects, CMV infections are usually asymptomatic or manifest as a mild mononucleosis-like syndrome (2). Gastrointestinal (GI) CMV infection is rarely seen in this group; thus, clinically significant GI CMV infection generally occurs in immunocompromised patients (3), like patients with inflammatory bowel disease (IBD) who are under long-term immunosuppressive treatment. CMV infection in the GI tract may develop in all locations, from the mouth to the rectum, and it generally manifests with formation of ulcers on the mucosa, frequently accompanied by hemorrhage (1). In immunocompromised IBD patients, the risk for CMV infection rises, although it does not always lead to clinically active disease (19) or the necessity of treatment.

The pathogenic role of CMV among ulcerative colitis (UC) patients remains unclear. It has been claimed that its prognosis is generally poor (4-6). However, the real significance of CMV infection on top of the active mucosal inflammation is not yet fairly documented. Therefore, it is not clear whether mucosal inflammatory activity arises mainly from severely active IBD or the additive effect of CMV infection. Clinical symptoms of CMV infection in UC patients are indistinguishable from those of a UC relapse. Thus, the patients are often misdiagnosed and treated with corticosteroids. Therefore, at least in patients with UC who do not respond to conventional medical treatment, it is necessary to consider the possibility of CMV infection and initiate preemptive therapy in severely active patients (7).

Identifying the cases with CMV colitis among patients with severe, steroid-refractory IBD is important, as a number of open design studies report that anti-viral treatment can dramatically improve the course of CMV-associated colitis and prevent colectomies (8-11).

The prevalence of CMV enterocolitis in IBD patients was generally studied in retrospective trials, yielding estimated rates of 19-44% among patients with severe refractory disease (10,12,13), whereas estimated rates were just 0.5-3.4% in patients with active, non-refractory disease (4,12). However, in patients operated for UC, the prevalence of CMV enterocolitis is higher (4.6%) (15). Available literature claims that the diagnostic accuracy of tissue biopsy sampling is high when histopathology is combined with immunohistochemistry (IHC) (16).

Establishment of latent or subclinical CMV infection prior to immunomodulating therapy is not essential and does not constitute a contraindication for treatment. Unfortunately, immunomodulating therapy is usually associated with subclinical reactivation of latent CMV infection (16). This reac-

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tivation is generally asymptomatic or manifests with a mild, self- limiting disease, and severe tissue damage is observed rarely (17,18). Based on uncontrolled studies, in subclinical cases or mild symptomatic reactivations, no treatment is required and there is no need to discontinue immunomodulating therapy. These cases generally go unnoticed and recover spontaneously.

In IBD cases refractory to immunosuppression, the accepted gold standard in the diagnosis of CMV colitis is either polymerase chain reaction (PCR) or IHC. CMV infection (detected by serology or viral DNA) should be differentiated from CMV disease causing end-organ damage. In patients treated with immunomodulating agents presenting with severe colitis and CMV in the mucosa, antiviral treatment should be initiated and immunomodulating therapy should be suspended until symptoms are alleviated. According to the above information, which is mainly based on uncontrolled clinical observational studies and case reports, the clinical significance of CMV colitis is still not clear. Therefore, to evaluate the value of diagnostic tools in colonic CMV disease and the necessity of treatment, a systematic literature search was conducted in the PubMed database including English written case reports and clinical trials.

MATERIALS AND METHODS

Designated questions for our literature search were as follows: 1-What is the prevalence of CMV infection among UC patients? 2- What are the predictive factors for development of CMV infection among these patients? 3-What is the ideal treatment for CMV infection, and what is the rate of spontaneous recovery? Keywords used were as follows: "Colitis, Ulcerative"[Mesh] AND ("Cytomegalovirus"[Mesh] OR "Cytomegalovirus Infections"[Mesh]), "Crohn Disease"[Mesh] AND ("Cytomegalovirus"[Mesh] OR "Cytomegalovirus Infections"[Mesh]), "Inflammatory Bowel Diseases"[Mesh] AND ("Cytomegalovirus"[Mesh] OR "Cytomegalovirus Infections"[Mesh]). All the literature assessed was written in English and dated between 1980 and 2010. Studies published in other languages were excluded from the analysis. A total of 204 literature results were traced; 145 reports were excluded following title/abstract screening and 17 reports were excluded after full text review. The remaining 41 literature reports were analyzed. Among these trials, 11 had a prospective design, five had a retrospective design, and there were three case series and 22 case reports.

RESULTS

The results of the present study were established on prospective and retrospective trials where the diagnosis of CMV colitis was based on IHC or tissue PCR positivity. Prevalence and risk factors of CMV colitis are shown in Table 1 and Table 2, respectively. Odds ratios (ORs) of the risk factors, such as sex, steroid use, azathioprine (AZA) use, cyclosporine use, extension of colitis, and existence of endoscopically active disease are shown in Table 3.

The distribution of the female/male ratio in the case reports and case series was 45%/55%. This was not documented in all retrospective and prospective studies. However, according to the documented reports, the female/male (55%/45%) ratio does not seem to be different than the sum of case reports.

In our literature search, age was available only in case reports and case series; therefore, the mean

Table 1. CMV positivity in IBD patients by means of immunohistochemistry and polymerase chain reaction in intestinal biopsies in retrospective and prospective trials

CMV (+)	IHC	Tissue PCR
Prospective	*11% (range: 1%-57%)	**27% (range: 4%-78%)
Retrospective	***13% (range: 3%-25%)	****37% (range: 12%-56%)

*References: 4, 7, 11, 14, 19-25 **References: 10, 15, 26-29 ***References: 10, 12, 13, 15, 16 ****References: 12, 13
CMV: Cytomegalovirus IHC: Immunohistochemistry PCR: Polymerase chain reaction

Table 2. The percentage of the use of various drugs among IBD patients with CMV colitis

	Steroid	AZA	5-ASA	CyA	Infliximab
*Prospective	86% (range: 25%-100%)	22% (range: 21%-50%)	4.6%	28% (range: 10%-100%)	2.6%
**Retrospective	96% (range: 61%-100%)	10%		2%	2%

AZA: Azathioprine. 5-ASA: 5-Aminosalicylic acid. CyA: Cyclosporine A. *References: 1-9, 11, 14, 17 **References: 10, 12, 13, 15, 16

age was 28.9±19.24 years (range: 15-72 years). This was a decade older in prospective and retrospective studies. However, age and disease duration were found to be insignificant variables regarding the prevalence of CMV colitis in previous reports (2,4,6-9).

Description of CMV colitis is not clearly documented in prospective, retrospective and case series. In the clinic, CMV may present itself with leukopenia and/or thrombocytopenia (29) in addition to other findings. In our retrospective analysis of cases individually, the authors indicated the leukocyte count during the follow-up of the diagnostic period in only 20 out of 52 case reports. In this respect, we noted 7 patients with leukopenia and thrombocytopenia, 6 patients with leukocytosis and 6 patients with normal leukocyte count. Equal distribution of colectomy rates between patients with and without leukopenia indicates that leukopenia does not seem to have any effect on the clinical ending.

In CMV-positive case series, until the diagnosis of CMV colitis, 82% of patients were treated with steroids, 31% with AZA, 50% with 5-ASA, 23% with cyclosporine, and 9.8% with infliximab. Evaluation of combined use of immunosuppressive agents revealed that 41% of patients were being treated with steroid+5-ASA, 27% were using steroid+AZA, 23% steroid+CyA, 15% AZA+5-ASA, 9.8% 5-ASA+CyA, 7.8% AZA+CyA, 5.8% steroid+infliximab, 3.9% AZA+infliximab, 3.9% 5-ASA+infliximab, and at least 1.9% CyA+infliximab (Table 4).

Analysis of doses and duration of treatment among patients revealed that steroids were used in doses of 30 mg-1 g for 10 days - 3 years, AZA as 50 mg-200 mg for 1 year - 39 months, CyA as 4 mg/kg/day for 3-10 days, infliximab as 5

Table 3. Risk factors for developing CMV enterocolitis in IBD patients

Risk factors	*(Prospective) OR	CI	**(Retrospective) OR	CI
Steroid	6.8	95% CI: 3.893-12.092 p: 0.00	12.6	95% CI: 4.427-36.387 p: 0.00
AZA	1.5	95% CI: 0.946-2.449 p: 0.09	1.7	95% CI: 0.514-5.781 p: 0.09
CyA	10.4	95% CI: 5.786-18.974 p: 0.00		
Pancolitis	1.8	95% CI: 1.07-3.114 p: 0.02		
Female	1.1	95% CI: 0.757-1.851 p: 0.49	0.2	95% CI: 0.041-1.794 p: 0.34
Male	1.1	95% CI: 0.745-1.787 p: 0.57	3.6	95% CI: 0.557-24.133 p: 0.34
Active colonoscopy	3.3	95% CI: 1.109-9.840 p: 0.02		

AZA: Azathioprine. CyA: Cyclosporine A. OR: Odds ratio. CI: Confidence interval. *References: 1- 9, 11, 14 **References: 10, 12, 13, 15, 16

Table 4. The percentage, dose and treatment duration of the use of various drugs among case reports with CMV colitis in IBD patients

Drugs	Percentage	Dose	Duration	Combination	Percentage
Steroid	82%	30 mg-1 g	10 days-3 yrs	Steroid+5-ASA	41%
AZA	31%	50-200 mg	1 yrs-39 mos	Steroid+AZA	27%
5-ASA	50%	1200 mg-4 g	1 wk-39 mos	Steroid+CyA	23%
CyA	23%	4 mg/kg/day	10 days-3 yrs	AZA+5-ASA	15%
Infliximab	9.8%	5 mg/kg/day	4 mos-1 yrs	5-ASA+CyA	9.8%
				AZA+CyA	7.8%
				Steroid+infliximab	5.8%
				AZA+infliximab	3.9%
				5-ASA+infliximab	3.9%
				CyA+infliximab	1.9%

AZA: Azathioprine. 5-ASA: 5-Aminosalicylic acid. CyA: Cyclosporine A. wk: Week. yrs: years. mos: months.

mg/kg/day for 4 months - 1 year, and 5-ASA as 1200 mg-4 g for 1 week - 39 months (Table 4).

The ratios of ganciclovir or foscarnet use or percentages of patients treated surgically or followed without treatment are shown in Table 5. Analysis of case reports revealed a higher rate of ganciclovir use among cases (82%). Foscarnet use was as low as 1.9% and valganciclovir use was 9.8%, and 21% of patients were treated surgically. In 11% of patients, medical treatment failed, and 5.8% of cases were followed without treatment.

CONCLUSION

Patients with IBD typically have a chronic, relapsing-remitting course. Patients are often persistently exposed to steroids and immunosuppressant agents and thus become susceptible to infection. However, the clinical impact of CMV disease on active UC is still difficult to evaluate. Several studies have assessed CMV positivity in surgical specimens among UC patients who underwent colectomy, and found a strong relationship between CMV colitis and steroid-refractoriness or development of toxic megacolon. Kambhan et al. (15) compared the histopathological features of steroid-responsive and steroid-refractory UC patients and showed that CMV colitis was significantly more prevalent in refractory patients, and several studies found high prevalences of CMV colitis among IBD patients with active disease, ranging from 15.8-27.1% (5,19).

Several methods are currently used for detecting CMV infection. For the diagnosis of GI CMV, combined CMV antigenemia assay and detection of CMV inclusion bodies in biopsy specimens from the GI mucosa either by hematoxylin and eosin (HE) or IHC have been proposed (19). It is often difficult to diagnose CMV infection in patients with UC, even when using this combined method. Several recent studies indicate that the real-time tissue PCR assay allows more sensitive and rapid detection of CMV-DNA in clinical samples, and is more useful and beneficial for diagnosis of CMV infection than CMV antigenemia assay or histologic examination (8,18). However, IHC and tissue PCR may yield varying rates of CMV in IBD patients; therefore, it is not clear which technique describes the potential clinical manifestation. Furthermore, whether tissue PCR positivity of CMV is more clinically relevant than serum PCR positivity has not been shown yet. The possibility of detecting CMV in IBD patients is increased in parallel to use of steroids and cyclosporine. The state of being refractory to steroids may be more meaningful as compared to dose and duration of steroids. It is possible to determine CMV concentration in cases found as CMV positive by IHA, but the clinical relevance is not clear.

Leukopenia and thrombocytopenia may either be an indicator of systemic CMV signs, including CMV colitis, or side effects of immunomodulators, like AZA and methotrexate (MTX), etc. Although this interpretation needs to be done by the physician on a clinical basis, the value of this point has not been studied in IBD clinics yet. Furthermore, equal distribution of leukopenia, with or without thrombocytopenia, and leukocytosis during the diagnostic follow-up of case reports makes it a non-significant parameter in the prognosis of CMV colitis. Finally, leukopenia and thrombocytopenia do not seem to predict the success of medical treatment and colectomy rates.

Among the immunosuppressives that are believed to increase the vulnerability for opportunistic infection, like CMV colitis, steroid was the longest used drug with largest dose range. Others, like AZA, cyclosporine and infliximab, had more narrow and stable dose ranges than that of steroid in clinical use. Retrospective analysis of infectious complications of medical treatment of IBD, including CMV, also clearly indicates that steroid use is the most important single factor for opportunistic infections, although combination with immunomodulators and infliximab may increase the opportunistic infection rates.

Regarding the need for surgery, there is a great similarity in colectomy rates among prospective, retrospective trials and case reports, although the use of antiviral agents like ganciclovir or foscarnet

Table 5. Percentage of different treatment modalities in IBD patients with CMV enterocolitis

Treatment	Ganciclovir	No treatment	Surgery	Foscarnet
*Prospective	8% (range: 8%-75%)	46% (range: 25%-100%)	30% (range: 3%-100%)	
**Retrospective	34% (range: 7%-70%)	38% (range: 14%-92%)	32% (range: 7%-29%)	4%

*References: 1-9, 11, 14 **References: 10, 12, 13, 15, 16

is much higher among case reports. This could be due to delay in introducing the treatment in relation to the more meticulous assessment of patients in case base or overestimation of the severity of the clinical condition. However, similar colectomy rates among the prospective and retrospective trials and case reports may give us a clue about the nearly similar severity of CMV colitis in all three groups. Furthermore, the natural course of CMV colitis may not have been positively affected by antiviral treatment to the extent we expect to see.

In this literature review, in all groups (prospective–retrospective trials or case reports), one- third of CMV-positive patients were referred to surgery, and clinical improvement and/or final surgery rate in cases with anti-viral treatment was not shown to be superior to non-treated cases. However, the existing data regarding which cases in clinical practice should be treated are chaotic and insufficient. Therefore, in severely active patients refractory to steroids, a "treat and follow-up" approach for CMV positivity may be recommended to prevent potential unnecessary clinical applications, like hesitating to use immunomodulators/anti-tumor necrosis factor or sending a patient for immediate colectomy.

Recommendations:

What is the prevalence of CMV infection among UC patients?

The presence of CMV among patients with IBD is variable with IHC and PCR. It is not clear which one defines the active clinical picture. Positive serum CMV DNA may not indicate the clinically relevant active disease. ***(EL 2b, RG B)***

What are the predictive factors for development of CMV infection among these patients?

The possibility of an active CMV infection (disease) increases in IBD patients who are under steroids and/or cyclosporine treatment. When compared to dose and duration of steroids, the state of being refractory to steroids may be more decisive. ***(EL 2b, RG B)***

What is the ideal treatment for CMV infection, and what is the rate of spontaneous recovery?

Existence of systemic disease findings and gradual increase in the basal serum CMV DNA titration in the sequential assays may be decisive for the anti-viral treatment. Ganciclovir is the first-line choice in the anti-viral treatment. ***(EL 5, RG D)***

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